REMARKS

Claims 1-49 were previously canceled. Claims 50-54 are pending. Applicants respectfully request reconsideration of claims 50-54 in view of the comments herein.

Double Patenting Rejection

Claim 50 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 and 6 of copending Application No. 12/391,157.

The Examiner has cited copending Application No. 12/391,157 in a provisional obviousness-type double patenting rejection. No terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. *See* MPEP 804 (I)(B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional double patenting rejection is the only rejection remaining in at least one of the applications"). In the event that other rejections of the present claims are successfully overcome by the current communication, the current obviousness-type double patenting rejection would then be the sole remaining rejection, and withdrawal of the instant provisional rejection would be appropriate.

Applicants therefore respectfully requests deferral of response to the provisional double patenting rejection until allowable subject matter has been indicated. Applicants authorize the examiner to follow MPEP 804 (I)(B) and allow the case without issuing a further Office Action should the provisional obviousness type-double patenting rejection be the sole remaining issue in the case.

Rejection Under §112

1. Enablement (First Paragraph)

The Examiner has rejected claims 50-54 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner has asserted that the present disclosure does not enable one skilled in the art to make and use the inventions as claimed. The Examiner asserts that undue experimentation would be needed to practice the claims and provides arguments on the basis of each of eight *Wands* factors. Applicants address each of the factors individually below.

A. Breadth of the Claims

The Examiner asserts that the claims are broad, encompassing multiple inhibitors of prolyl-specific DPP. Applicants do not dispute the Examiner's reading of the breadth of the claims. However, certain implications of the Examiner's statement regarding breadth of the claims are addressed below under analysis of the other *Wands* factors.

B. Nature of the Invention

The Examiner characterizes the nature of the invention as a method of determining a treatment regimen including the use of a prolyl-specific DPP inhibitor. The Examiner further notes that the specification discloses the method of action of DPP inhibitors (preventing degradation of mature BNP) and that such inhibition improves the therapeutic value of mature BNP. Applicants do not dispute the Examiner's contentions. However, Applicants also add that the specification discloses, in multiple instances, antibodies that specifically bind to, and detect mature BNP (77-108), versus other species of BNP (*see, e.g.,* paragraphs [0016], [0026], [0036]). Furthermore, the specification discloses the utility of using such specific antibodies in achieving a correct clinical assessment of the active form of BNP, versus the combination of active and inactive (i.e., cleaved) forms (see, e.g., paragraphs [0052] and [0082]-[0086]. Thus, the specification discloses both a method of detecting the active and clinically useful form of BNP, as well as using that detection to guide therapeutic choices.

C. State of the Prior Art

The Examiner discusses the disclosures of multiple references, including Haffner (US Pub. No. 2004/0167341) and Scharpe (US Pub. No. 2002/0061839). Applicants agree with the Examiner regarding the lack of guidance in Haffner regarding use of a DPP inhibitor and levels of any species of BNP. Applicants respectfully disagree with the Examiner's assessment of the importance of the teachings of Scharpe. As the Examiner recognized, Scharpe teaches the use of DPP IV inhibitors used in conjunction with therapy of acute myocardial infarction. Although Scharpe disclosed the inhibition of Factor X, thrombin and Factor VII, Applicants note that one of skill in the art would readily recognize that a DPP IV inhibitor provided to a patient will prevent the action of that enzyme on any target, such as mature BNP. Thus, the disclosure of Scharpe, contrary to the Examiner's position, demonstrates that one of skill in the art would recognize therapeutic and treatment regimens using DPP inhibitors. Of course, Scharpe does not disclose the use of immunoassays which specifically detect mature BNP or use that analysis to guide decision making in a clinical setting.

The Examiner also briefly mentions Cheng et al. (*J. Am. Coll. Cardio* (2001) 37:386-391) as describing the use of full-length BNP molecule "marker for various diseases". Applicants disagree with the Examiner's assessment of the teaching of Cheng. As indicated in the abstract of this reference, clinicians at the time of publication recognized the value of testing for levels of mature BNP in guiding treatment for congestive heart failure. (see "Conclusions" section of abstract). What was not recognized at the time, was that older assays for BNP did not distinguish between active forms (e.g., mature BNP) and inactive forms (e.g., cleaved BNP). Applicants were the first to discover antibodies and immunoassays using those antibodies which could distinguish between the active and inactive forms. As discussed above, the present application discloses the use of such immunoassays to guide therapeutic decisions based on determination of the active form.

Applicants also note that the present application also mentions the Gault et al reference, which discloses the clinical use of DPP inhibitors (see, paragraph [0133]). Thus, one of skill in

the art would have known how to prescribe DPP inhibitors and treat patients with these inhibitors.

D. Level of One of Ordinary Skill in the Art

The Examiner asserts that the level of one of skill in the art is high. Applicants disagree with this assessment. The claims recite a method of determining a treatment regimen, based in part on a diagnostic test. Such determinations are routinely made by physicians from the beginning of their careers. As such, the level of one of ordinary skill in the art is merely that of a physician with less than one year of experience.

E. Level of Predictability in the Art

The Examiner asserts that the level of predictability in the art is extremely low. Applicants disagree with this assessment. As discussed above, one of skill in the art, familiar with the teachings of the art would have known: 1) how to prescribe DPP inhibitors for the management of disease; and 2) that measurement of BNP levels could be used to determine treatment course for a patient with congestive heart failure. Applicants provide the novel and non-obvious step of using antibodies and immunoassays which allow for precise measurement of the active (i.e., clinically beneficial mature form) form of BNP. Thus, contrary to the Examiner's position, the predictability of using Applicants' immunoassays to guide therapeutic decisions is high.

F. Amount of Direction Provided By the Inventor(s)

The Examiner asserts that Applicants have provided little direction to allow for one of skill in the art to successfully practice the disease. In particular, the Examiner notes that only "a general description on how DPP inhibitors operate *in vivo* with no concrete direction or steps on how to effectuate such inhibition." (Office Action, pg. 9). Applicants respectfully disagree that such information is missing from the record. As the Examiner recognizes, the art references cited are replete with examples of the operation of DPP inhibitors *in vivo*, for example the use of

DPP inhibitors to treat diabetes described by Gault et al. One of skill in the art would recognize that DPP inhibitors would operate *in vivo* to inhibit DPP's activity on any target (including BNP). Applicants recognize that different dosages of a given DPP inhibitor may need to be provided to a subject in order to inhibit degradation of BNP, however, changing dosages of a medicament is well within the abilities of one of skill in the art. Thus, one of skill in the art would recognize that a DPP inhibitor which works *in vivo*, will function to prevent degradation of targets of the enzyme (e.g., BNP) and only dosages might need to be modified.

G. Existence of Working Examples

The Examiner asserts that there are no working examples showing that a DPP inhibitor actually prevents degradation of BNP *in vivo*. Applicants disagree with this assessment. As discussed above, one of skill in the art would recognize that a DPP inhibitor functions to inhibit DPP. DPP-IV, for example, targets multiple substrates, one of which in BNP. Thus, the art of record provides sufficient guidance for one of skill in the art to use DPP inhibitors at sufficient levels to inhibit the function of DPP.

The Examiner further asserts that the specification appears to lack disclosure on the relationship between detection of BNP and a treatment regimen. Applicants again disagree with this assessment. At least in paragraphs [0082]-[0086] the present disclosure provides the rationale of use and discussion of the use of antibodies which can be used to determine the level of functional BNP and relate that to therapeutic decisions. As described above, the clinical use of DPP inhibitors and their modulation to achieve a desired clinical result would have been recognized by one of skill in the art at the time of filing.

The Examiner also asserts that no guidance is provided on the amount of mature BNP or what amount or manner of treatment would comprise the treatment regimen. As already discussed above, both of these aspects were known in the art at the time of filing. What was not known, and what is provided by the Applicants is an accurate immunoassay for the specific detection of mature (i.e., clinically relevant) BNP.

H. Quantity of Experimentation Needed

The Examiner asserts that a great deal of experimentation would be needed. As already discussed above, a DPP inhibitor inhibits the enzymatic activity of DPP. Such inhibition would affect all targets of DPP, including BNP. Furthermore, DPP inhibitors were in clinical use and described in the cited art. Additionally, the cited art described the use of analyses of BNP levels to guide therapeutic choices in treating congestive heart failure. Applicants clearly describe the use of immunoassays to specifically detect active, mature BNP. Thus, the only "experimentation" necessary to practice the inventions as disclosed and claimed would be the modification of specific doses to achieve desired clinical outcomes. Such modification of dosages are well within the skill of one in the art and do not require only standard, routine experimentation.

2. Summary

As discussed above, the present application, in light of the teachings of the prior art would allow one of skill in the art to successfully practice the claimed inventions. Applicants respectfully submit that the Examiner's focus on an alleged lack of showing of function of DPP inhibitors in vivo is in error. Inhibitors of DPP function on the enzyme, preventing its action on its targets. Furthermore, one of skill in the art, in light of the art of reference would be able to prescribe and modify a treatment regimen for a subject in need of treatment with a DPP inhibitor. A novel and non-obvious aspect of the invention presently claimed is the use of immunoassays which are able to specifically detect the level of mature BNP, which is not disclosed in the art. Thus, Applicants respectfully submit that the present application provides sufficient guidance for one of skill in the art to successfully practice the claimed invention. Therefore, for at least the above reasons, the present claims are enabled and allowable. Applicants respectfully request withdrawal of the rejection of claims 50-54 under Section 112, first paragraph and allowance of the claims.

CONCLUSION

Applicants respectfully submit that all rejections and objections have been obviated and that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for an additional action.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16 1.17, or credit any overpayment, to Deposit Account No. 23-2415 (36671-744.502). If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extensions under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 23-2415.

Respectfully submitted,

By _____
Mark D. McNemar, Esq., Ph.D.
Reg. No. 64,904

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WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304
Telephone No.: (650) 493-9300